

In the abstract:

Please substitute the abstract, attached hereto, for the abstract appearing on page 1 of the application papers.

II. REMARKS

Claims 75-77, 81-83, 88, 92-107, 109-111 and 118-132 were pending in the application. Claims 75-77, 81-83, 88, 92-107, 109-111 and 118-132 were rejected in the March 23, 1998 Office Action. By virtue of this Amendment, claims 75-77, 81-83, 88, 98-103, 105-107, 109-111, and 118-132 have been amended. Claims 92-97 and 104 are canceled without prejudice or disclaimer. The cancellation of these claims and the amendment of the claims are not intended to be a dedication to the public of the subject matter of the claims as previously presented. Applicants reserve their right to file one or more continuing application on the same or similar claims under 35 U.S.C. § 120. Claims 133-138 are added. Accordingly, claims 75-77, 81-83, 88, 98-103, 105-107, 109-111, and 118-138 are currently under examination.

Applicants acknowledge withdrawal of finality of the previous Office Action mailed July 23, 1997, in light of Applicants' request under 37 C.F.R. § 1.129(a), filed on January 23, 1998. Applicants also acknowledge withdrawal of the previous rejections (set forth in the Office Action mailed July 23, 1997) under 35 U.S.C. § 112, second paragraph, 35 U.S.C. §§ 102(e)/103(a) and the judicially-created doctrine of obviousness-type double patenting; in light of Applicants' amendments and remarks presented in their Response of January 23, 1998.

Rejections Under 35 U.S.C. § 112, Second Paragraph

All pending claims stand rejected under this section as allegedly indefinite. Applicants address each of the rejections, in turn.

A. Claims 118-129 stand rejected as depending from cancelled claims. Applicants thank the Examiner for pointing out this problem with claims 118-129. The claims have been amended to remove the improper dependency.

B. Claims 75-77, 81-83, 88, 92-97, 101-107, 109-111 and 118-132 stand rejected as allegedly indefinite over the recitation "said chromophore or fluorophore attached." It is stated that it is unclear as to where, how and to what the label is attached.

In a sincere effort to overcome this ground of rejection, the claims have been amended to recite in part "coupled chemically" to more clearly point out and distinctly claim the subject matter which Applicants regard as their invention. This amendment is supported in the specification at page 9, lines 10-11, wherein it is stated: "[e]ach of these tags is coupled chemically to the primer . . ." In addition, Applicants note that page 9, lines 21-23 recites that "[t]he chromophore or fluorophore must not interfere with the hybridization or prevent 3'-end extension by the polymerase" which is consistent with the Examiner's interpretation of the claim. Accordingly, one of skill in the art, upon reading the claim and the specification would know how and where the chromophore or fluorophore should be attached to the primer, i.e., so that it would not interfere with 3'-end extension.

C. Claims 75-77, 81-83, 92-107, 109-111 and 118-130 stand rejected as allegedly indefinite over the recitations "has been base-paired to a template" and "has been separated." It is stated that it is unclear as to whether the claims are drawn to an oligonucleotide primer itself, or a primer extended and/or hybridized to a template. It is further stated that the use of the phrase "has been" renders the claims indefinite because it is unclear exactly when the primer was base-paired or extended or separated.

In response to this rejection and without conceding the correctness of the Examiner's position, the claims have been amended to remove the offending language and to more clearly point out and distinctly claim that a duplex of a primer and template is claimed; that the template

is extended by a polymerase, and that the extended primer can be removed from the template to generate an oligonucleotide. Support for the claim amendments can be found on page 9, lines 19 to 23 of the specification.

D. Claims 98-100 stand rejected as indefinite, as it is alleged that it is unclear as to whether the claims encompass an oligonucleotide with a first portion, an oligonucleotide with first and second portions, or an oligonucleotide with first and/or second portions and/or a template.

In response, and without conceding the correctness of the Office's position, claim 98 has been amended to recite a single-stranded oligonucleotide comprising first and second portions. Accordingly, withdrawal of this rejection is respectfully requested.

E. Claims 101-107, 109-111 and 130-132 stand rejected as allegedly indefinite because the phrase "a primer" in the phrase "providing a primer" allegedly lacks antecedent basis.

In response, claim 101 has been amended to recite the duplex of claim 75. In light of the amendment of claim 75 to recite a duplex, and the amendment of claim 101 to recite the duplex of claim 75, Applicants request withdrawal of this rejection. Proper antecedent basis for the primer of claim 101 is found in its parent claim 75.

F. Claims 101-107, 109-111 and 130-132 stand rejected as allegedly indefinite. It is stated that it is unclear how the steps of providing a tagged primer and hybridizing the primer to a complementary sequence constitute a method of making a primer according to claim 75.

In light of the amendment to claim 75 to recite a duplex, and the amendment to claim 101 to recite a method for making the duplex of claim 75 by hybridizing a primer to a template, Applicants believe that the Examiner's concerns regarding definiteness have been addressed, and request withdrawal of this rejection.

G. Claims 101-107, 109-111 and 130-132 stand rejected as allegedly indefinite over the recitation "hybridizing the primer to a sequence which is complementary." It is stated that it is unclear what "a sequence" refers to.

In response, and to more particularly point out and distinctly claim the invention, claim 101 has been amended to recite a "template" rather than a "sequence." Support for the term "template" is found in the specification on page 3, line 14 and page 11, lines 9 to 27.

H. Claims 94, 97, 100, 103 and 107 stand rejected as allegedly indefinite over the recitation "5' end or in the vicinity thereof." It is asserted in the Office Action that vicinity is a relative term that does not adequately describe the metes and bounds of the claim

Applicants respectfully traverse and direct attention to the specification at page 9, lines 21-23, wherein it is stated: "[t]he chromophore or fluorophore must not interfere with the hybridization or prevent 3'-end extension by the polymerase." Thus, when claim 94, stating that "the primer is tagged at its 5' end or in the vicinity thereof" is interpreted in light of the teaching of the specification, it is clear that the vicinity of the 5' end is meant to denote a location that is sufficiently distant from the 3' end that it will not prevent 3' end extension by the polymerase.

I. Claims 105-107 and 109-111 stand rejected as allegedly indefinite over the recitation "the method comprising extending the primer of claim 101" as this phrase is alleged to lack proper antecedent basis.

The claims have been amended in a sincere effort to remove this ground for rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

J. Claims 109-111 stand rejected as allegedly indefinite over the recitation "a method comprising use of the oligonucleotide of claim 105." It is stated that the role of the oligonucleotide in claim 105 is unclear.

Applicants respectfully traverse. The oligonucleotide of amended claim 105 is clearly defined as a chemically coupled, extended primer that has been separated from its template.

Such oligonucleotides are routinely generated in chain termination sequencing methods.

Accordingly, Applicants request withdrawal of this rejection.

K. Claims 110 and 111 stand rejected as allegedly indefinite over the recitation "the performance," as it is stated that this phrase lacks proper antecedent basis.

In response, and to more particularly point out and distinctly claim the invention, the claims have been amended as noted above. Reconsideration and withdrawal of the rejection is respectfully requested.

L. Claim 111 stands rejected as allegedly indefinite over the recitation "the primer includes all four chain termination DNA sequencing reactions." It is stated that it is unclear if the primer has, in its sequence, all of the chain terminating ddNTPs or if the primer is to be used in the presence of each chain terminating ddNTP so as to contain only one type of ddNTP.

In response, Applicants point out that that the claim recites that the chemically coupled oligonucleotides produced from four different duplex sets are distinguishable, one from the other, by the spectral characteristics of the attached chromophore or fluorophore. This recitation would make it clear to one of skill in the art that each set is produced using a differently labeled primer, in the presence of a different ddNTP. Accordingly, Applicants request withdrawal of this rejection.

In sum, Applicants submit that the foregoing amendments and remarks address and overcome all ground for rejection of the claims under 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of the grounds for rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

A. Claims 75-77, 81-83, 88, 92-107, 109-111 and 118-132 stand rejected as allegedly obvious over Kitamura et al. (1980) *Proc. Natl. Acad. Sci. USA* 77:3196-3200, in view of Smith et al. U.S. Patent No. 5,171,534.

Prior to addressing the substance of the rejection, Applicants note that the statement on page 7 of the Office Action, to the effect that the inventive entity of the Smith reference (*i.e.*, the '534 patent) is different from that of the instant invention, is incorrect. Applicants enclose, for the Examiner's consideration, a Decision on Petition issued by the Office on December 3, 1996, in U.S. Patent No. 5,171,534. The decision grants a petition to amend the inventive entity of U.S. Patent No. 5,171,534 to Smith, Hood, M. Hunkapiller, T. Hunkapiller and Connell, which is the same inventive entity as that of the instant invention. Accordingly, the application of U.S. Patent No. 5,171,534 against the pending claims is improper.

Due to the withdrawal of the application of U.S. Patent No. 5,171,534, Applicants submit that the Office has not set forth a *prima facie* case of obviousness of the rejected claims. Reconsideration and withdrawal of the rejection is respectfully requested.

B. Claims 75-77, 81-83, 88, 92, 94, 95, 97, 98, 100, 101, 103-105, 107, 109, 119, 120, 122, 123, 125, 126, 128, 129, 131 and 132 stand rejected as allegedly obvious over Kitamura et al. in view of Langer et al. (1981) *Proc. Natl. Acad. Sci. USA* 78:6633-6637 and further in view of Leary et al. (1983) *Proc. Natl. Acad. Sci. USA* 80:4045-4049. The Office asserted that that Kitamura teaches that the use of an end-labeled primer *in lieu* of labeled nucleotides improved the results by reducing background and cost. With respect to Langer, the Office asserts that this reference teaches a biotin label as a suitable alternative to radioisotopes for nucleic acid detection, that avidin coupled to an indicator molecule (such as a fluorescent dye) will specifically detect a biotinylated oligonucleotide, that modified nucleotides are

substrates for polymerases, and that oligonucleotides containing biotinylated nucleotides are capable of specific and efficient hybridization to complementary sequences. With respect to Leary, the Office asserts that this reference teaches methods for making biotinylated hybridization probes by nick-translation.

Applicants note that the primers of Kitamura are RNA primers derived from the poliovirus genome. Thus, the method described by Kitamura is applicable only in a limited number of special cases involving sequence determination of RNA genomes. The use of RNase A- and RNase T1-resistant oligonucleotides for sequencing primers, as described by Kitamura, is not a general method for either primer extension or sequence determination.

However, even if the method of Kitamura could be generalized, its combination with the techniques of Langer and Leary would not be capable of generating tagged oligonucleotides according to the present invention, for the following reasons. Applicants note that probes comprising Langer's biotinylated nucleotides require reaction with labeled avidin for detection. By contrast, the tagged oligonucleotides of the invention are inherently detectable by virtue of their chromophore or fluorophore. Hence, if the radioactively-labeled primer of Kitamura were substituted by a biotin-labeled primer according to Langer, it would still not form an inherently detectable oligonucleotide, as recited in the present invention. Instead, detection of such a biotin-labeled primer would require, at the very least, the additional steps of reacting the biotin labeled primer with labeled avidin and washing to remove unreacted labeled avidin.

With respect to Leary, Applicants wish to point out that the claimed invention requires a defined-sequence primer. See page 3 of the specification at lines 16-19: "[t]he primer is either a synthetic oligonucleotide or a restriction fragment . . ." Both synthetic oligonucleotides and restriction fragments are molecules with a defined sequence. It is impossible to make a defined sequence primer by the nick translation method of Leary. As is known to those of skill in the art, nick translation inserts an unpredictable number of labeled nucleotides at random positions in a

nucleic acid and generates a labeled product that is heterogeneous in size (and, therefore, is also heterogeneous in sequence). Furthermore a double-stranded substrate is required for nick translation, while it is well-known to those of skill in the art that a primer must be single-stranded. Denaturation of a nick-translated DNA molecule would generate a heterogeneous collection of fragments, unsuitable for use as a primer. Finally, the primers described by Kitamura are RNA primers and nick translation will not work with an RNA template. Thus, even if the theoretical biotinylation of Kitamura's primers would have generated tagged probes equivalent to those recited in the invention, (which it would not, see above), it would be impossible to make such biotinylated Kitamura primers using the method of Leary. Moreover, even if it were possible, introduction of a different and unpredictable amount of label into different primers, as would be achieved by the method of Leary, would risk interfering with 3'-end extension of said primers. *See* the specification at page 9, lines 21-23.

Accordingly, Applicants submit that the combination of Kitamura, Langer and Leary do not make obvious the present invention, and respectfully request withdrawal of this rejection.

Supplemental IDS

On March 13, 1998, Applicants filed a Supplemental IDS for the subject application. Applicants respectfully request acknowledgement of this Supplemental IDS and entry and consideration of the cited reference.

III. CONCLUSION

Applicants, by virtue of this Response, have addressed the concerns outlined in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. Should the Examiner feel that a telephone conversation would expedite

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disposition of this application, she is invited to contact the undersigned at the telephone number listed below.

In the unlikely event that the transmittal letter is separated from this document and/or the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 243132000105. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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